Complete Summary

GUIDELINE TITLE

Assessment: botulinum neurotoxin in the treatment of autonomic disorders and pain (an evidence-based review). Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology.

BIBLIOGRAPHIC SOURCE(S)

Naumann M, So Y, Argoff CE, Childers MK, Dykstra DD, Gronseth GS, Jabbari B, Kaufmann HC, Schurch B, Silberstein SD, Simpson DM, Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Assessment: Botulinum neurotoxin in the treatment of autonomic disorders and pain (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2008 May 6;70(19):1707-14. [34 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Hypersecretory disorders
  - Axillary hyperhidrosis
  - Palmer hyperhidrosis
  - Gustatory sweating
  - Drooling in neurodegenerative diseases
  - Hyperlacrimation
- Neuro-urologic disorders

    - Detrusor sphincter dyssynergia
    - Neurogenic detrusor overactivity
- Low back pain
- Headache
    - Episodic migraine
    - Chronic daily headache
    - Chronic tension-type headache

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Technology Assessment
Treatment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Neurology
Pharmacology
Physical Medicine and Rehabilitation
Urology

INTENDED USERS

Pharmacists
Physicians

GUIDELINE OBJECTIVE(S)

- To perform an evidence-based review of the safety and efficacy of botulinum neurotoxin (BoNT) in the treatment of autonomic and urologic disorders and low back and head pain
- To make evidence-based recommendations

TARGET POPULATION

- Adult patients with autonomic and urologic disorders
- Adult patients with low back pain and headache

INTERVENTIONS AND PRACTICES CONSIDERED

Botulinum neurotoxin (BoNT) injection

MAJOR OUTCOMES CONSIDERED

- Response rate (reduction in sweating; reduction in drooling)
- Quality of life
- Post-voiding residual urine volume
- Urethral or detrusor pressure
- Urodynamic measures

- Urinary frequency and average voided volume
- Level of pain
- Functional improvement
- Frequency of moderate to severe migraines per month
- Headache-free days per month

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The literature search used MEDLINE and Current Contents for relevant, fully published, peer-reviewed articles up to April 2007 and was supplemented through manual searches by panel members. The search terms used were botulinum toxin and movement disorders, dystonia, tics, tremors, hemifacial spasm, blepharospasm, cerebral palsy, spasticity, autonomic, Frey's syndrome, sweating, hyperhidrosis, drooling, headache, back pain, pain, laryngeal disorders, dysphonia, and urologic disorders. The following criteria were used: 1) relevant to the clinical questions of efficacy, safety, tolerability, or mode of use; 2) limited to human subjects; 3) limited to therapeutic studies. Abstracts, reviews, and meta-analyses were excluded.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Classification of Evidence for Therapeutic Intervention

Class I: Randomized, controlled clinical trial with masked or objective outcome assessment in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. The following are required: a) concealed allocation, b) primary outcome(s) clearly defined, c) exclusion/inclusion criteria clearly defined, and d) adequate accounting for drop-outs (with at least 80% of enrolled subjects completing the study) and cross-overs with numbers sufficiently low to have minimal potential for bias.

Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets b-d above OR a randomized controlled trial in a representative population that lacks one criteria a-d.

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.*

Class IV: Studies not meeting Class I, II, or III criteria, including consensus, expert opinion, or a case report.

*Objective outcome measurement: An outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The panel was comprised of specialists with experience in the therapeutic use of botulinum neurotoxin (BoNT) for the indications under consideration or with expertise in guideline methodology. Each article was reviewed by at least two panelists who did not participate in the trial reported. The articles were classified as Class I through IV using the American Association of Neurology (AAN) guideline process (see "Rating Scheme for the Strength of the Evidence"). Disagreements on article classification were resolved by discussion and consensus.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Other

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Conclusions and recommendations were made according to the American Academy of Neurology (AAN) criteria for translating the quality of evidence for therapeutic interventions into recommendations.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Classification of Recommendations

The strength of practice recommendations is linked directly to the level of evidence:

Level A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.*)

Level B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

Level C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or at least two consistent Class III studies)

Level U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven. (Studies not meeting criteria for Class I–Class III).

* In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met and/or 2) the magnitude of effect is large (relative rate improved outcome >5 and the lower limit of the confidence interval is >2.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Draft guidelines were reviewed for accuracy, quality, and thoroughness by the American Academy of Neurology members, topic experts, and pertinent physician organizations.

The guideline was approved by the Therapeutics and Technology Assessment Subcommittee on March 31, 2007; by the Practice Committee on July 12, 2007; and by the American Academy of Neurology (AAN) Board of Directors on January 30, 2008.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Definitions of the levels of the recommendations (A, B, C, U) and classification of the evidence (Class I through Class IV) are provided at the end of the "Major Recommendations" field.

Hypersecretory Disorders

Conclusions

Botulinum neurotoxin (BoNT) is established as safe and effective for the treatment of axillary hyperhidrosis (**two Class I studies**), is probably safe and effective for

palmar hyperhidrosis (**two Class II studies**) and in drooling in patients with Parkinson's disease (PD) (**four Class II studies**), and is possibly effective for gustatory sweating (**five Class III studies**). There is insufficient evidence to support the effectiveness of BoNT in hyperlacrimation (**Class IV studies**).

Recommendations

- BoNT should be offered as a treatment option to patients with axillary hyperhidrosis (**Level A**).
- BoNT should be considered as a treatment option for palmar hyperhidrosis and drooling (**Level B**).
- BoNT may be considered for gustatory sweating (**Level C**).

Neuro-urologic Disorders

Conclusions

BoNT is established as safe and effective for the treatment of neurogenic detrusor overactivity in adults (**two Class I studies, one Class II study**). Data on the use of BoNT for detrusor sphincter dyssynergia (DSD) are conflicting. BoNT is probably safe and effective for the treatment of DSD in patients with spinal cord injury (**two Class II studies**). However on the basis of one Class I study, BoNT does not provide significant benefit for the treatment of DSD in patients with multiple sclerosis (MS).

Recommendations

- BoNT should be offered as a treatment option for neurogenic detrusor overactivity (**Level A**).
- BoNT should be considered for DSD in patients with spinal cord injury (**Level B**).

Low Back Pain

Conclusions

BoNT is possibly effective for the treatment of chronic predominantly unilateral low back pain (LBP) (**one Class II study**).

Recommendation

BoNT may be considered as a treatment option of patients with chronic predominantly unilateral LBP (**Level C**).

Headache

Episodic Migraine

Conclusions

Based on published **Class I** and **Class II studies**, BoNT injection is probably ineffective in the treatment of episodic migraine (**Level B**).

Chronic Daily Headache

Conclusions

Based on inconsistent results from **four Class II studies**, there is insufficient evidence to support or refute a benefit of BoNT for the treatment of chronic daily headache (**Level U**).

Chronic Tension-type Headache

Conclusions

Based on the results of **two Class I studies**, at least one of which was adequately powered, BoNT injection is probably ineffective for patients with chronic tension-type headaches (**Level B**).

Recommendation

BoNT injections should not be considered in patients with episodic migraine and chronic tension-type headaches (**Level B**).

Definitions:

Classification of Recommendations

Level A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.*)

Level B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

Level C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or at least two consistent Class III studies)

Level U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven. (Studies not meeting criteria for Class I–Class III).

* In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met and/or 2) the magnitude of effect is large (relative rate improved outcome >5 and the lower limit of the confidence interval is >2.

Classification of Evidence for Therapeutic Intervention

Class I: Randomized, controlled clinical trial with masked or objective outcome assessment in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. The following are required: a) concealed allocation, b) primary outcome(s) clearly defined, c) exclusion/inclusion criteria clearly defined, and d) adequate accounting for drop-outs (with at least 80% of enrolled subjects completing the study) and cross-overs with numbers sufficiently low to have minimal potential for bias.

Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets b-d above OR a randomized controlled trial in a representative population that lacks one criteria a-d.

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.*

Class IV: Studies not meeting Class I, II, or III criteria, including consensus, expert opinion, or a case report.

*Objective outcome measurement: An outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of botulinum neurotoxin for treatment of autonomic disorders and pain

POTENTIAL HARMS

- Undesirable effects associated with administration of botulinum neurotoxin (BoNT) fall into three broad categories. First, diffusion of the toxin from the intended sites of action can lead to unwanted inhibition of transmission at neighboring nerve endings. Second, sustained blockade of transmission can

produce effects similar to anatomic denervation, including muscle atrophy. The third undesirable effect is immunoresistance to BoNT.

- Adverse events reported for BoNT in the treatment of autonomic disorders and pain include:
  - Mild or transient muscle weakness
  - Pain at the injection site
  - Dry mouth
  - Urinary retention
  - Ptosis
  - Diplopia
  - Bruising
  - Local skin tension
  - Flu-like symptoms

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

This statement is provided as an educational service of the American Academy of Neurology (AAN). It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved. The clinical context section is made available in order to place the evidence-based guildeline(s) into perspective with current practice habits and challenges. No formal practice recommendations should be inferred.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Patient Resources
Quick Reference Guides/Physician Guides
Slide Presentation
Staff Training/Competency Material

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Naumann M, So Y, Argoff CE, Childers MK, Dykstra DD, Gronseth GS, Jabbari B, Kaufmann HC, Schurch B, Silberstein SD, Simpson DM, Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Assessment: Botulinum neurotoxin in the treatment of autonomic disorders and pain (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2008 May 6;70(19):1707-14. [34 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2008 May 6

GUIDELINE DEVELOPER(S)

American Academy of Neurology - Medical Specialty Society

SOURCE(S) OF FUNDING

American Academy of Neurology (AAN)

GUIDELINE COMMITTEE

Therapeutics and Technology Assessment Subcommittee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Primary Authors: M. Naumann, MD; Y. So, MD, PhD; C.E. Argoff, MD; M.K. Childers, DO, PhD; D.D. Dykstra, MD, PhD; G.S. Gronseth, MD; B. Jabbari, MD; H.C. Kaufmann, MD; B. Schurch, MD; S.D. Silberstein, MD; D.M. Simpson, MD

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The American Academy of Neurology (AAN) is committed to producing independent, critical and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guidelines have been reviewed by at least three AAN committees, a network of neurologists, *Neurology*® peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com.

The authors report the following conflicts: Dr. Naumann has received speaker honoraria from Ipsen and Allergan and performs botulinum toxin injections. Dr. So holds financial interest in Satoris Inc., and has received research support from NIH, Pfizer, Inc., and NeurogesX, Inc. Dr. Argoff performs botulinum toxin injections. Dr. Childers has received speaker honoraria and research support from Allergan and performs botulinum toxin injections. Dr. Dykstra has received speaker honoraria from Allergan and Solstice, research support from Allergan, and performs botulinum toxin injections. Dr. Gronseth has received speaker honoraria from Pfizer, GlaxoSmithKline, Boehringer Ingelheim, and Ortho-McNeil. Dr. Jabbari has received research support from Allergan and performs botulinum toxin injections. Dr. Kaufmann has received speaker honoraria from Chelsea Therapeutics, research support from NIH, payment for expert testimony, and performs autonomic testing. Dr. Schurch has received speaker honoraria from Pfizer, Astellas, and Allergan; research support from Allergan, IFP, NCCR, and SNF; and performs autonomic testing and botulinum toxin injections. Dr. Silberstein has received speaker honoraria from GlaxoSmithKline, Allergan, AstraZeneca, Endo, Medtronic, Merck, J&J, Pfizer, Pozen, and Valeant Pharmaceuticals International; research support from Allergan, and performs botulinum toxin injections. Dr. Simpson has received speaker honoraria and research support from Allergan, Merz, and Solstice, Inc., and performs botulinum toxin injections.

ENDORSER(S)

American Academy of Physical Medicine and Rehabilitation - Medical Specialty Society

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: A list of American Academy of Neurology (AAN) guidelines, along with a link to a Portable Document Format (PDF) file for this guideline, is available at the AAN Web site.

Print copies: Available from the AAN Member Services Center, (800) 879-1960, or from AAN, 1080 Montreal Avenue, St. Paul, MN 55116.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Use of botulinum neurotoxin for the treatment of autonomic disorders and pain. AAN summary of evidence-based guidelines for clinicians. St. Paul (MN): American Academy of Neurology. 2008. 2 p. Available in Portable Document Format (PDF) from the AAN Web site.
- Assessment: botulinum neurotoxin for the treatment of autonomic disorders and pain, movement disorders, and spasticity (an evidence-based review). Slide presentation. St. Paul (MN): American Academy of Neurology. 2008. 146 p. Available from the AAN Web site.
- Assessment: botulinum neurotoxin for the treatment of autonomic disorders and pain, movement disorders, and spasticity (an evidence-based review). Case study and coding. St. Paul (MN): American Academy of Neurology. 2008. 3 p. Available from the AAN Web site.
- AAN guideline development process [online]. St. Paul (MN): American Academy of Neurology. Available from the AAN Web site.

PATIENT RESOURCES

The following is available:

- Use of botulinum neurotoxin injections to treat autonomic disorders and pain. AAN summary of evidence-based guideline for patients and their families. St. Paul (MN): American Academy of Neurology (AAN). 2008. 2 p.

Electronic copies: Available in Portable Document Format (PDF) from the AAN Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This summary was completed by ECRI Institute on November 3, 2008. The information was verified by the guideline developer on December 30, 2008.

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